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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/803,954	02/21/97	LANGLEY K	0109063/004

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EXAMINER	
HAYES,R	
ART UNIT	**PAPER NUMBER**
1645	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/803,954	Langley et al
Examiner	**Group Art Unit**
Robert C. Hayes	1645

☒ Responsive to communication(s) filed on *Nov 18, 1998*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-4, 6, 7, 9-11, 31, 32, 34, and 37-43* is/are pending in the application.

Of the above, claim(s) *34, 38, and 39* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4, 6, 7, 9-11, 31, 32, 37, and 40-43* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-4, 6, 7, 9-11, 31, 32, 34, and 37-43* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Amendment

1. The amendments filed 11/18/98 and 7/14/99 have been entered.

2. The objection under 37 CFR 1.75 of claim 1 being a substantial duplicate thereof of claim 2 is withdrawn because different posttranslational modifications of the protein of claim 1 are possible with prokaryotes versus eukaryotes; thereby, not necessarily being the same protein.

3. The rejection of claim 32 under 35 U.S.C. 112, second paragraph, as being indefinite and incomplete is withdrawn due to the amendment to the claim.

4. The rejection of claims 1-4, 6-7, 9-11 & 31-32 under 35 U.S.C. 102(b) as being anticipated by Murray et al., is withdrawn due to the amendment of the claims to human metalloprotease inhibitor "comprising at least the amino acids residues 1 to 42 of Figure 2", versus the native *bovine* metalloprotease inhibitor, TIMP-2.

5. The rejection of claims 1-4, 6-7, 9-11, 31-32 & 37 under 35 U.S.C. 102(e) as being anticipated by Stetler-Stevenson et al. (US Patent 5,595,885), is withdrawn due to Applicant's arguments and the amendment of the claims.

6. Applicant's arguments filed 11/18/98 have been fully considered but they are not deemed to be persuasive.

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claim 1 is objected to because reciting sequences by Figure number, versus by the appropriate SEQ ID NO fails to comply with the Sequence rules. Appropriate correction is required.

9. Applicant is again advised that should claim 1 be found allowable, claims 4, 6-7 & 9-10 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof, for the reasons made of record, and as follows.

In contrast to Applicants' assertions on page 5 of the response, in each of these cases the same protein is being claimed. Even though the process may be different, the physical and functional characteristics of the protein claimed is identical; thereby, being duplicative. Applicants' arguments are, therefore, not persuasive. See MPEP § 706.03(k).

Applicants are again reminded in that because parent application no. 07/355,027 is at the Board of Appeals, and because the Examiner does not have access to the pending claims on

appeal, a double patenting rejection may be necessitated if those claims are directed toward metalloprotease inhibitor protein products, as in the instant application.

10. Claims 1-4, 6-7, 9-11, 31-32, 37 and new claims 40-43, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the bovine and human TIMP-2 proteins of Figures 1 & 2, respectively, does not reasonably provide enablement for biologically functional equivalents, or undescribed allelic variants of these TIMP-2-like proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the reasons made of record and as follows.

Analogous to that previously made of record, the new limitations of merely possessing 42 amino acids of the human TIMP-2 of Figure 2, still encompasses any biologically functional equivalent or allelic variant of the "mature" TIMP-2 protein, or any randomly mutated or randomly truncated form of a protein with "metalloprotease inhibitor" activity, because a protein with only 42 structurally defined amino terminal amino acids still sets for little structural or functional characteristics that distinguishes the claimed protein from any different metalloprotease inhibitor-related protein. Similarly, the protein of claim 37 possesses no recited structural and little functional characteristics. The metes and bounds of the recitation, "has at least one biological activity of naturally-occurring human metalloprotease inhibitor", is also unknown, and therefore, does not sufficiently define any protein. Accordingly, because those specific amino

acids critical for metalloprotease inhibitory function are unknown, not disclosed and not recited in the claims, it would prevent the skilled artisan from knowing how to make and use the instant invention, as currently claimed, without requiring undue experimentation to determine such; consistent with the teachings of Rudinger previously made of record. In addition, a protein comprising only 42 known amino acids, or a protein that merely possesses an immunological activity to some unknown and undefined epitope of a structurally deficient metalloprotease inhibitor, would not reasonably possess the activity of the human protein of Figure 2; thereby, further preventing the skilled artisan from determining how to make and use Applicants' invention, as currently claimed, for the reasons made of record. Further, in that any biologically functional equivalent molecules, are also still encompassed by the current claim language, it was held in *Ex parte Maizel* (27 USPQ2d 1662 at 1665) that:

> Appellants have not chosen to claim the DNA [product] by what it is but, rather, by what it does, i.e., encoding either a protein exhibiting certain characteristics, *or* a biologically functional equivalent thereof. Appellants' claims might be analogized to a single means claim of the type disparaged by the Court of Customs and Patent Appeals in *In re Hyatt,* 708F.2d 712, 218 USPQ 195 (Fed. Cir. 1983). The problem with the phrase "biologically functional equivalent thereof" is that it covers any conceivable means, i.e., cell or DNA, which achieves the stated biological result while the specification discloses, at most, only a specific DNA segment known to the inventor. Clearly the disclosure is not commensurate in scope with the claims."

Thus, the issue remains the specification provides insufficient guidance on how to make and use the generic metalloprotease inhibitors of the instant invention, as currently broadly claimed, because it is unknown and not disclosed structurally what amino acids that can be

substituted, truncated, etc. in such generic metalloproteinase inhibitor with little recited structural or functional characteristics, without requiring undue experimentation to determine such, for the reasons made of record.

Applicants' arguments, therefore, are not persuasive for the reasons made of record.

11. Claims 1-4, 6-7, 9-11, 31-32, 37 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unknown what metes and bounds are encompassed by the recitation, "has at least one *biological activity* of naturally-occurring human metalloprotease inhibitor", in that it is unknown what such undefined "*in vitro* biological activity" entails; thereby, being indefinite.

12. Claim 37 is again rejected under 35 U.S.C. 102(b) as being anticipated by Murray et al., for the reasons made of record and as follows.

In contrast to Applicants' assertions on pages 8-9 of the response, no structural limitations that distinguish Murray's native bovine metalloprotease inhibitor (i.e., TIMP-2 that is free of other proteins and inherently at least 95% pure; pg. 4158, Table III) are recited in claim 37. Thus, Murray's TIMP-2 protein still anticipates claim 37, for the reasons made of record.

13. Claims 1-4, 6-7, 9-11, 31-32, 37 & 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stetler-Stevenson et al. (US Patent 5,698,671) (i.e., the straight continuation from priority application no. 07/326334 in US Patent 5,595,885).

Stetler-Stevenson et al. teach isolation and direct partial amino acid sequencing of a native human 23,000 Dalton metalloprotease inhibitor, TCCI (i.e., TIMP-2), which is free of other proteins, either glycosylated or nonglycosylated, and is inherently at least 95% pure with no pyrogen present, as evidenced by the single amino acid sequences obtained, the single band obtained on a 15% polyacrylamide gel under reducing conditions (e.g., col.3, lines 48-52), as well as the disclosure of "purified" in cols.3-4 (i.e., as it relates to claims 1, 3, 31 & 37). Column 2 and Figure 1 indicates that this metalloprotease inhibitor has the biological activity of inhibiting type IV collagenase (i.e., as it relates to claims 1, 10 & 42), and therefore, reasonably also inhibits type 1 collagenase (i.e., as it relates to claim 43); absent evidence to the contrary. In that this protein is immunogenic in generating anti-peptide antibodies (col.4, lines 9-15), the limitations of claims 1, 9 & 41 are met. In that pharmaceutical compositions comprising this protein are disclosed in columns 4 and 6, the limitations of claim 32 are met. In that purified TCCI peptides "can be tagged with suitable enzymatic, fluorescent or radioactive labels" (col. 5), the limitations of claim 32 are also anticipated.

However, the sole differences in sequence between Stetler-Stevenson's TIMP-2 protein and the 42 amino acid peptide of the instant invention is the conservative substitution of Pro to Asp at position #34, and a conservative substitution back to Pro from an Asn at position #39, in

which amino acids 40 and 41 were also not sequenced. It is noted that the complete sequence disclosed in Figure 2 is not being claimed in this application, in contrast to Applicant's arguments on page 10 of the response.

Thus, because human TIMP-2 is human TIMP-2, because Stetler-Stevenson discloses that "[a]nalogs of the natural inhibitor of the invention can be made by preparing peptides and proteins having cysteines at the same intervals as the cysteines in the natural inhibitor (e.g., col.3, lines 8-15), and because these two conservative changes can be considered merely allelic/analog differences between Stetler-Stevenson's TIMP-2 protein and that currently claimed, these two amino acid substitutions between these two human TIMP-2 peptides are considered a *de minimus* change that would not affect any intrinsic TIMP-2 activity, as evidenced by the metalloproteinase inhibitor function Stetler-Stevenson's TIMP-2 peptide possesses (e.g., cols. 2 & 4); thereby, not being patentably distinct, and hence obvious, analogous to that held in *Ex parte Anderson, 30 USPQ2d, 1867 (1994).*

It is also noted that the courts have held that when a product (i.e., TIMP-2) in a product-by-process claim (i.e., being synthetic or made recombinantly; col.4, lines 49-62; as it relates to claims 2, 4, 6-7 & 40) is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process (*In re Thorpe.*, 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983). Further, the courts have held that "when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product..., a rejection based

alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable". *In re Brown*, 173 USPQ 685 (1972).

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert C. Hayes, Ph.D.
October 1, 1999

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